REVIEW

Childhood and Adolescent Anxiety and Depression: Beyond Heritability

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Objective: To review the methodology of behavior genetics studies addressing research questions that go beyond simple heritability estimation and illustrate these using representative research on childhood and adolescent anxiety and depression. **Method:** The classic twin design and its extensions may be used to examine age and gender differences in the genetic determinants of complex traits and disorders, the role of genetic factors in explaining comorbidity, the interaction of genes and the environment, and the effect of social interaction among family members. An overview of the methods typically employed to address such questions is illustrated by a review of 34 recent studies on childhood anxiety and depression. **Results:** The review provides relatively consistent evidence for small to negligible sex differences in the genetic etiology of childhood anxiety and depression, a substantial role of genetic factors in accounting for the temporal stability of these disorders, a partly genetic basis of the comorbidity between anxiety and depression, a possible role of the interaction between genotype and the environment in affecting liability to these disorders, a role of genotype-environment correlation, and a minor, if any, etiological role of sibling interaction. **Conclusion:** The results clearly demonstrate a role for genetic factors in the etiology and temporal stability of individual differences in childhood anxiety and depression. Clinical implications of the findings are discussed. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(8):820–829. **Key Words:** childhood and adolescent anxiety/depression, genotype-sex interaction, genotype-age interaction, genotype-environment interaction, genotype-environment correlation

An important role of twin and family studies in psychiatry has been to establish the contributions of genetic and environmental factors to observed or phenotypic individual differences in psychiatric disorders. Genetic research, often employing the classic twin design, has demonstrated the pervasive importance of genetic and environmental factors in complex psychiatric disorders and related traits (e.g., personality). These findings can be seen as guiding molecular genetic studies that have become so prevalent, because there would be no use in searching for genes that influence individual differences in behavior if those individual differences were not shown to be influenced at least in part by genetic factors. Twin studies have evolved, however. At present, due to developments in statistical methods and the establishment of large twin registries in which measured genotypes and environmental variables are available, psychiatric genetic research is moving beyond the relatively simple task of assessing the contributions of genetic and environmental factors. Current research often focuses on more subtle issues, such as how genetic and environmental influences are modulated by age and sex or how gene expression is affected by the environment that an individual is reared in.

In the present article we review the recent findings of genetic research in the area of childhood and adolescent anxiety and depression. The aim is not to provide a comprehensive overview of all the existing literature, but to introduce the reader to the methods used in behavior genetics while presenting the results of representative research relevant to the current key issues. To

This article is discussed in an editorial by Drs. James J. Hudziak and Stephen V. Faraone on page 729.

TABLE 1 Decomposition of variance into genetic and environmental components

Expression	Meaning
$V = h^2 + c^2 + e^2$	Standardized phenotypic variance, i.e., variance of an observed trait (V=1) consisting of variance due to additive genetic factors (h^2), variance due to shared environmental factors (c^2), and variance due to unique environmental factors (e^2)
$r_{MZ} = h^2 + c^2$	Correlation between MZ twins
$r_{DZ} = ½\ h^2 + c^2$	Correlation between DZ twins
$h^2 = 2(r_{MZ} - r_{DZ})$	Proportion of phenotypic variance explained by genetic factors (i.e., the heritability coefficient)
$c^2 = r_{MZ} - h^2$	Proportion of phenotypic variance explained by shared environmental factors
$e^2 = 1 - r_{MZ}$	Proportion of phenotypic variance explained by unique environmental factors

Note: DZ = dizygotic; MZ = monozytic; V = phenotypic variance.

this end, we introduce the classical twin design and a number of recent extensions thereof. These extensions serve to address specific issues, which we discuss in the context of recent research findings. The issues include sex and age differences in the genetic etiology of childhood anxiety and depression, the nature of the comorbidity of these disorders, the interplay between genes and the environment, and social interactions among family members. We conclude with a discussion of the clinical implications of recent findings.

Classic Twin Design and Heritability Estimation

The classical twin design is used to decompose phenotypic variance (the statistical term to quantify variation or individual differences) in one or more traits into components due to additive genetic (A), shared environmental (C), and unique environmental (E) factors. We assume that the additive genetic variance is attributable to the contribution of an unspecified number of genes, and the environmental variance to the contribution of an unspecified number of environmental events. In humans, each gene (or locus) consists of two alleles, one contributed from the mother and one from the father. The alleles may be the same (the individual is a homozygote), or parents may contribute different alleles (the individual is a heterozygote). The term *additive* reflects the assumption that the contribution of each allele to the effect of the gene on the phenotype is additive. We may also distinguish dominance effects, which result from interactions (i.e., nonadditive effects) of alleles at a given locus. However, because dominance effects are rarely seen in genetic studies of anxiety and depression,[1] we limit our discussion to additive genetic effects. Shared environmental factors constitute influences that increase the observed similarity between family members. Unique environmental factors constitute environmental influences that cause family members to differ.

The phenotypic variance (the total variance of a trait or disorder), which we denote V_P, can be decomposed as follows: $V_P = V_A + V_C + V_E$. The contributions of V_A, V_C, and V_E can also be expressed as proportions, i.e., as the ratios of V_A, V_C, and V_E to the total phenotypic variance: $h^2 = V_A/V_P$, $c^2 = V_C/V_P$, and $e^2 = V_E/V_P$. Thus, if the total phenotypic variance is standardized (V=1), it can be expressed as $V = h^2 + c^2 + e^2$. The correlation between monozygotic (MZ) twins arises because they share their additive genetic (as they arise from a single fertilized egg) and common environmental influences. Therefore the correlation between MZ twins can be expressed as $r_{MZ} = h^2 + c^2$. On average, dizygotic (DZ) twins share 50% of their genes, and therefore the DZ twin correlation can be expressed as $r_{DZ} = ½\ h^2 + c^2$. Based on the twin correlations, we arrive at the following simple estimate of the contribution of additive genetic factors to the phenotypic variance: $h^2 = 2(r_{MZ} - r_{DZ})$. This estimate is known as the heritability coefficient. Table 1 also details the estimation of c^2 and e^2.

For the classical twin design to yield correct and generalizable estimates of genetic and environmental influences, several assumptions have to hold.[2-5] For instance, it is assumed that environmental influences are identical in MZ and DZ twins. This assumption has been challenged on the grounds of evidence showing that MZ twins experience more similar environments than DZ twins. However, with regard to environmental aspects relevant to psychopathology, it has been

shown that greater environmental sharing in MZ twins is a consequence, rather than a cause, of their phenotypic similarity.[4] Furthermore, it is assumed that the results obtained by studying twins generalize to non-twin populations. This assumption appears to hold, as estimates of environmental and genetic influences found in twin studies differ very little from those found in non-twin studies.[4] Other assumptions include the absence of assortative mating (the tendency to mate with individuals with a phenotype similar to one's own), of genotype-environment interaction (dependency of genetic effects on the environment and vice versa), and of genotype-environment correlation (nonrandom placement of genotypes in the range of available environments). These effects may be assessed and, when assumptions are not met, can be modeled if the appropriate data are available.

In addition, because twin data alone do not provide enough information to estimate the variance attributable to shared environmental factors and the variance attributable to dominance genetic factors, in the classical twin design one has to choose whether to estimate the shared environmental variance and assume the dominance genetic variance is zero, or estimate the dominance genetic variance and assume the shared environmental variance is zero. This choice is typically informed by inspecting the pattern of MZ and DZ correlations for the trait under study. A DZ correlation greater than half the MZ correlation suggests an effect of shared environment on the trait; a DZ correlation smaller than half the MZ correlation suggests genetic dominance.

Beyond Heritability

Using the classical twin design, researchers have established the role of genetic and environmental factors in virtually all psychiatric traits. Currently, due to several developments that took place over the last half of the past century, it is possible to move beyond the basic question of heritability. These developments include the large-scale collection of phenotypic data by well-validated standardized questionnaires, and the collection of extensive genotypic (i.e., DNA) and environmental data. Furthermore, the realization that the resolution of relatively subtle effects requires large samples has provided the impetus for the establishment of large twin and family registries.[6] In the case of children, survey data obtained from teachers, in addition to parental ratings, form an important source of information concerning childhood development and psychopathology. Another important development has been the possibilities offered by advances in statistical and psychometric modeling.

Given these developments, researchers are now looking into more subtle aspects of genetic and environmental effects. These include the dependency of these effects on sex and age. Age or developmental effects are important in understanding the role of genetics in the development of psychopathology; also, such effects negate the perception of the heritability of a given phenotype or disorder as a fixed entity. In addition, the availability of measured genotypes and environmental variables allows researchers to address the largely neglected issue of genes-by-environment interaction (GEI) in the development of psychopathology. Finally, given the genetic data, researchers are increasingly turning to the detection of individual genes associated with particular phenotypes by linkage and genomewide association (GWA) studies.[7,8]

Sex Differences in the Genetic Architecture of Anxiety and Depression

Does the heritability of a disorder differ between the sexes? Are the genetic effects in males and females attributable to the same genes, whose affects are possibly modulated by sex, or to different genes? The former suggests a quantitative sex difference in the genetic architecture; the latter, a qualitative difference. These questions, which may also be posed with respect to environmental effects, may be addressed within the framework of the twin design.

Quantitative and qualitative sex effects may result in sex differences in the estimated genetic and environmental variance components. Quantitative differences are apparent when estimates of genetic and environmental variances differ in girls and boys. Qualitative differences can be resolved by testing whether the genetic correlation in opposite-sex DZ twins is significantly different from the expected value based on the correlations of same-sex DZ twins. The finding that this correlation is lower than expected (i.e., that opposite-sex DZ twins genetically resemble each other less than same-sex DZ twins) suggests that the risk factors affecting males and females are different (i.e., the genetic sex differences are

qualitative). An analogous method can be used to establish whether different shared environmental factors are implicated in the trait in males and females.

The applications of this methodology to childhood anxiety and depression have generally revealed small to negligible differences in heritabilities for boys and girls. However, the results do appear to vary with the exact definition of the phenotype (e.g., general anxiety versus separation anxiety). In addition, the variation in results may depend on the measurement scale, i.e., on whether the phenotype is treated as a continuous variable or a dichotomy (e.g., affected versus not affected). Most studies included in the present review employed continuous measurements of anxiety and depression, defined as summed scores on standardized questionnaires such as the Child Behavior Checklist.[9] In case a categorical measurement of psychopathology (e.g., a diagnosis) is used, this is noted in the text. Finally, variation in age of the twins may also underlie the variation in the results.

Recently, Lamb et al. examined anxious depression and withdrawn behavior (as measured by the Youth Self-Report and divided into three categories) in 12-, 14-, and 16-year-olds, and found no evidence for different heritabilities in boys and girls.[10] Similarly, Rettew et al. studied neuroticism, a trait linked to anxiety and depression,[11] and found the genetic and environmental influences to be of equal importance in 12- to 17-year-old male and female adolescents.[12] The same result was obtained by Rice et al. for parental ratings of depression in 8- to 17-year-olds. For self-rated symptoms, however, the same study obtained evidence for greater genetic and lesser shared environmental influences in boys.[13] For separation anxiety in 3- to 18-year-olds, the opposite result was obtained, i.e., greater genetic and lesser shared environmental influences were found in girls.[14] A similar result was obtained by Happonen et al. using teacher ratings of depressive symptoms in 11- and 12-year-olds.[15] For self-, parent, and peer ratings, however, the same study found equal heritabilities between the sexes.

In addition, several recent studies have examined possible qualitative sex differences by establishing whether different or the same genes are expressed in girls and boys. Rettew et al. obtained some support for qualitative sex differences with respect to neuroticism in adolescent twins.[12] However, in a study of anxiety and depression in 3- and 12-year-olds, Boomsma et al. concluded that the same genes were being expressed in girls and boys.[16]

In conclusion, most studies have suggested that sex differences in the genetic architecture of childhood anxiety and depression, if present, are small. Because detection of sex effects may depend on other factors such as age and definition of phenotype, more research is needed to elucidate the role of such factors.

Age Differences in the Genetic Architecture of Anxiety and Depression

Genetic and environmental effects may be age-dependent. For instance, there is no reason to assume that environmental or genetic influences on anxiety or depression at age 5 years are identical to those at age 10 years. To establish such differences one can study twins who differ with respect to age. However, the correct interpretation of any established difference requires a study of twins in a longitudinal design, in which phenotypes are measured in the same twins at two or more occasions. Such data allow one to determine the role of genetic and environmental factors in the stability of individual differences over time. For instance, one may address the question whether the same genes contribute to individual differences over time, or whether shared environmental effects tend to diminish over time.

Studies of age-related changes in anxiety and depression have generally shown these disorders to be moderately stable during childhood. However, many children who initially display relatively high levels of anxiety or depression go on develop normally, whereas some other children, who displayed initial normal development, go on to develop anxiety or depression at a later age.[17] Furthermore, studies on age-related differences generally report an influence of shared environment on anxiety and depression during childhood that fades as children enter adolescence.[17-21] In adulthood, the influence of shared environment disappears, and the relative influence of genetic factors increases; as a consequence, the heritability of these traits increases with age. Similar results have been obtained for related phenotypes, such as withdrawn behavior and obsessive-compulsive symptoms.[10,22,23] A recent meta-analysis supported the increase in heritability of anxiety

and depression after childhood, and found this increase to be greater for anxiety-related symptoms than symptoms of depression.[24]

In addition, longitudinal studies have established qualitative age-related differences. In a study of anxious/depressed behavior as reported by parents, Boomsma et al. found relatively low stability of genetic effects on anxious depression in children of 3 to 7 years of age, and an increase in genetic stability from 7 to 12 years of age.[25] Kendler et al. reported that the same genes contribute to individual differences in anxiety and depression throughout the age span of 8 to 20 years.[26] However, they also found that additional, age-specific genetic influences emerge in adolescence and early adulthood. Hoekstra et al. assessed withdrawn behavior, a trait found to predict later anxiety and depression,[27] and found considerable stability of genetic influences throughout childhood.[28] Kendler et al. studied the development of situational, social, animal, and blood/injury fears, and found that genetic effects on these fears become more fear-specific as a function of age, and that in late adolescence new genetic influences relevant to social fears emerge.[29]

In summary, most longitudinal studies have reported a small to moderate temporal stability of childhood anxiety and depression. Although genetic factors appear to account for most of this stability, additional age-specific genetic factors have been found to emerge over time. However, the role of the informant remains a contentious issue. Estimates of genetic influences on psychopathology are known to depend on whether the data are obtained by self-report (obtained from the child itself) or from an informant such as a parent.[30] This is especially relevant for studies of age-related changes, because such studies often use informants (parent, teachers) to assess the behavior of young children, and self-report in older children.

Comorbidity

Twin design may be employed to address the question of whether the co-occurrence of two disorders has a genetic basis, an environmental basis, or results from a direct causal interaction between the disorders (e.g., depression directly causing anxiety). To address the question of comorbidity, the correlation between members of MZ and DZ twin pairs on *different* measures (e.g., depression in twin 1 and anxiety in twin 2) is calculated. A higher MZ correlation than DZ correlation is taken to indicate that the comorbidity has a genetic basis.

Multiple studies have demonstrated comorbidity within anxiety disorders and between anxiety disorders and depression, both in children and adults.[31,32] It has been shown that this comorbidity is explained partly by shared genetic risk factors.[33] For instance, Eley at al. studied five anxiety-related syndromes (general distress, separation anxiety, fears, obsessive-compulsive behaviors, and shyness/inhibition), and found moderate genetic overlap among these syndromes.[34] Silberg et al. found that depression in girls after age 14 years is genetically correlated with earlier symptoms of simple phobias and overanxious disorder, but environmentally correlated with separation anxiety.[35]

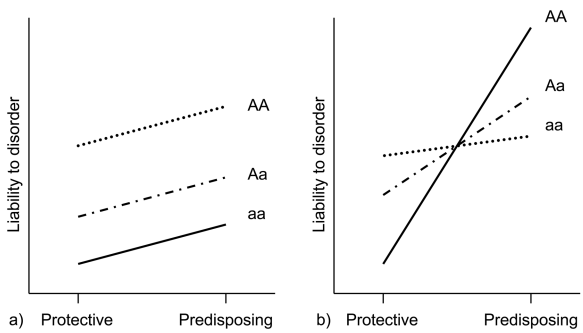
In addition, it is possible to test whether comorbidity results from one disorder directly causing the other. For instance, prolonged anxiety may lead to a depressive episode. If such a direct causal relation is present, then all genetic and environmental effects on the causal disorder will also be present in the "caused" disorder. A recent study of direct causal effects of exercise on depression in adults yielded no evidence for such direct causal effects.[36]

Genotype-Environment Interaction

Although genetic and environmental effects on childhood anxiety and depression have been well-established within the genetic epidemiologic literature, most studies have not examined how these factors combine in affecting liability to illness. It is frequently assumed, implicitly or explicitly, that genes and the environment affect the phenotype independently of each other. This is not necessarily the case.

For instance, assume an environmental factor, say an important life event, and a single gene with three possible genotypes, namely AA, Aa, and aa. If the life event increases the risk of disease to the same extent in individuals with any of these genotypes, the genotype and environment have an additive effect (Figure 1a).[37] However, if the average change in risk associated with the life event is different in individuals with different genotypes, the genotype and the environment interact (Figure 1b).[37] For instance, the liability of individuals with the AA genotype may increase substantially as a result of the life

FIGURE 1 Liability to a disorder as a function of genotype (AA, Aa, or aa) and environmental exposure (protective or predisposing). Note: The predisposing environment is associated with an increase in liability to develop a disease. (a) This increase is equal in individuals with the AA, Aa, and aa genotypes (additive effects). (b) The increase is different in individuals with different genotypes. Individuals with the AA genotype have a disproportionately lesser chance of developing a disease in the protective environment, but develop a disproportional increase in liability when exposed to the predisposing environment.[37]



event, whereas those with the aa genotype may barely be affected.

The most common way of investigating GEI is by estimating the relative effects of genetic and environmental factors on a trait across different levels of environmental exposure.[38] For instance, one can estimate the genetic and environmental contributions to depression in people with different levels of social support. If the genetic contribution to depression differs as a function of social support (say, heritability is higher in people with low levels of social support), this would constitute evidence for GEI. One may also estimate whether different genes are expressed across different levels of environmental exposure. This can be achieved using a twin design in which each participant is measured at two different levels of environmental exposure (e.g., before and after an important life event). The correlation between the measures taken in these two different conditions is partitioned into components due to genetic and environmental factors. If the component due to genetic factors is small, this suggests that different genes are expressed across different levels of the environmental exposure.[2]

Several recent studies of childhood psychopathology have obtained evidence for GEI.[39-41] For instance, Silberg et al. found greater genetic effects on anxiety/depression in adolescent girls who had experienced recent negative life events than in those who had not.[39] Similar findings were obtained for separation anxiety symptoms in childhood and panic anxiety symptoms in adolescence.[42] Lau and Eley found that 15-year-old adolescent girls at genetic risk for developing depression tended to experience more negative life events and maternal punitive discipline (an instance of genotype-environment correlation, addressed in the next section), and were at a higher risk of developing depressive symptoms in response to those events (GEI).[40] Feinberg et al. found no evidence for an interaction of parental negativity and warmth with heritability of interview-assessed depression in adolescents, but they showed that effects of an individual-specific environment on depression changed as a function of parental negativity.[43] As parental negativity increased, the effects of an individual-unique environment on depression increased. The latter finding is consistent with a recent study that examined the moderating role of six environmental factors (mother– and father–child relationship problems, antisocial and prosocial peer affiliation, academic achievement and engagement, and stressful life events), and found that the effects of an individual-specific environment on symptoms of depression and anxiety increased as environmental adversity increased.[44]

When measurements of the genotype are available, it is also possible to test for an interaction of the environment with a specific gene variant. In a now famous study, Caspi et al. investigated the association between the serotonin transporter gene and depression in adults who had experienced stressful life events and those who had not.[45] Stressful life events were associated with depression, but only in individuals who carried at least one copy of the short allele of the serotonin transporter gene promoter polymorphism. As influential as these results were, however, only a few studies have succeeded in reproducing them, and a meta-analysis of the main replication studies failed to produce significant evidence of an interaction between this polymorphism and stressful life events.[46]

It should be noted that the variation in the phenotype due to GEI, when not explicitly accounted for in statistical modeling, artificially increases the heritability estimate or the estimate of a unique environment.[47] In particular, the unac-

counted for variance due to the interaction of genotype and shared environment (A × C) inflates the estimate of heritability, whereas unaccounted for variance due to the interaction of genotype and a unique environment (A × E) inflates the estimate of variance due to unique environmental factors. If these are expected, but not explicitly modeled, these effects should be borne in mind when interpreting the results of twin studies.

Genotype-Environment Correlation

In the traditional twin design, the genetic and environmental contributions to individual differences are usually assumed to be independent or uncorrelated. However, the possibility of genotype-environment correlation (rGE) is widely recognized. In fact, three types of rGE are distinguished, namely passive, evocative, and active. *Passive rGE* refers to the case in which children inherit genes and an environment that predispose them to a given phenotypic outcome.[48] For an example of this, think of a parent who has depression. This parent may pass on genes that predispose the offspring to develop depression, but in addition may inadvertently create a depressogenic environment for the child (by being unresponsive, unhappy, demoralized, etc.). *Evocative rGE* refers to the situation in which person's genetically influenced characteristics evoke environmental reactions that exacerbate the characteristics.[49] For instance, an anxious and withdrawn child, simply by behaving anxious and withdrawn, may elicit certain responses in other children (e.g., shunning) or in parents (more protective parenting), which contribute to the child's anxiety. *Active rGE* refers to the situation in which individuals, as a consequence of certain characteristics, actively seek out or create environments that are conducive to these characteristics.[47,48] For instance, a withdrawn child may actively avoid social situations, such as birthday parties and sports activities, and thereby create an environment that fosters the child's general withdrawal.

One way to detect rGE is by decomposing the correlation between a measured environmental factor and the phenotype of interest into components due to A, C, and E factors. Any contribution of genetic factors to the observed correlation means that the same genetic factors are influencing the environmental phenotype and the trait, thus creating a correlation between the two.[48,49]

Several recent studies of childhood and adolescent anxiety and depression have obtained evidence for rGE. Kendler and Baker reviewed 55 studies and found that environmental variables, such as stressful life events, parenting, family environment, social support, peer interactions, and marital quality, are under significant genetic influence (with heritability estimates ranging from 0.07 to 0.39).[50] Narusyte et al. examined the association between maternal emotional overinvolvement and adolescent internalizing problems, and found no direct causal influence of maternal overinvolvement on adolescents' internalizing problems. However, they found that adolescents' (genetically influenced) internalizing problems evoked maternal overinvolvement.[51] Another study of parenting also found evidence for evocative rGE: temperamental traits of children, which are known to be subject to genetic influences, seemed to elicit parental warmth, protectiveness, and authoritarianism.[52]

It should be mentioned that the variance in the phenotype due to rGE, when not explicitly accounted for in statistical modeling, will lead to an overestimation of genetic or shared environmental effects. In particular, an unaccounted for correlation between A and C will increase C, whereas an unaccounted for correlation between A and E will increase the A estimate.[47]

Social Interaction Among Family Members

The MZ and DZ twins, like other siblings, continually interact as they grow up together. In this process the behavior of one sibling may influence the behavior of the other. If variance in the behavior of interest is in part genetic, then this implies that by their interaction, the genotypic factors of one sibling (i.e., his or her specific genotype) exert an influence on the phenotypic behavior of the other sibling.[53]

Such sibling interaction effects may be cooperative or competitive, depending on whether the behavior of one sibling facilitates or inhibits the behavior of the other. Cooperation, or positive interaction, leads to increased phenotypic MZ and DZ twin resemblance, whereas competitive or negative interaction will decrease it. In addition to this, sibling interaction affects the total phenotypic variance in MZ and DZ twins. If the interaction is cooperative and there is some genetic influence on the trait, the variance in MZ and DZ twins is increased, but the increase is greater in MZ twins. If the interaction is compet-

itive and there is genetic influence on the trait, MZ and DZ variabilities are decreased, but this decrease is greater in MZ twins. Therefore, depending on the pattern of MZ and DZ resemblance and the total phenotypic variance observed in MZ and DZ twins, interaction effects may be detected, and cooperative and competitive interaction distinguished.[53]

With respect to childhood anxiety and depression, studies have shown that sibling interaction effects play a minor, if any, etiological role. For instance, no evidence for sibling interaction effects on internalizing problems was found in 3-[54,55] and 10- to 15-year-old twins,[56] and to our knowledge only one study found some indication of twin contrast effects on separation anxiety and depression.[57] However, pervasive effects of sibling interaction has been demonstrated in externalizing disorders.[58]

DISCUSSION

Our review demonstrates the role of genetic factors in the etiology of depression and anxiety in the normal distribution. In so far as one subscribes to a dimensional model of psychopathology[59] in which affected children are considered to occupy the extreme of the population distribution, these results are strongly relevant. The implication of genetic factors per se clearly does not mean that the child's level of anxiety or depression is immutable, or that environmental interventions are essentially pointless. In fact, the implication is quite the opposite: the substantial heritability of anxiety may imply that the biological parents also display increased levels of anxiety, which could affect the child through passive rGE. This could mean that treatment should involve the parents and perhaps other siblings. Moreover, through reactive rGE, anxious and depressed children can elicit a certain parenting style, such as punitive discipline or overprotective behavior, which may in turn create an environment that sustains the symptoms. It is important to explain this mechanism to parents. Similarly, the child's diagnosis may stem from the interaction of a genetic predisposition and adverse environmental factors, such as divorce or being bullied at school. Such information further supports that a strategy aimed at improving the child's environment may yield improvements in the child's overall emotional behavioral health. Ultimately, once the relevant genes are identified and their function understood, one may be able to move toward an effective combination of personalized treatment that includes pharmacologic and environmental (family-based) interventions.

Identification of genetic variants through GWA studies has hardly been attempted for childhood traits. Two examples include a successful association study for fetal growth and birth weight and studies of childhood attention-deficit/hyperactivity disorder. Although attention-deficit/hyperactivity disorder studies need to be improved and replicated, they are starting to implicate processes such as neuronal migration and cell adhesion and division as potentially important in the etiology of attention-deficit/hyperactivity disorder.[60] For childhood anxiety and depression, no GWA studies currently exist, but several consortia such as the EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium[61] have been established. Some researchers have voiced major concerns at the feasibility of explaining heritability by GWA studies (the famous "missing heritability" problem) and a diversity of solutions has been proposed.[62] One solution might be the study of identical twins. The search for differences in genotypes within discordant MZ twin pairs seems to be a promising approach in gene finding. With future possibilities for human genome sequencing of large numbers of individuals, it may even become feasible to sequence large numbers of unselected MZ pairs, after which differences within pairs can be correlated with differences in phenotypes.[63]

As longitudinal studies have demonstrated, the chance that childhood anxiety or depression symptoms are transient is substantial; however, in case of persistent or recurrent symptoms, it is feasible to assume that genetic factors may play a greater role in their stability. We note that genetic factors may be correlated with environmental risk or could interact with an environment. In case of persistent symptoms, in addition to addressing environmental factors, therapy should focus on individual characteristics (such as attributional style, coping style, or the tendency to ruminate) that could maintain the symptoms.[64,65]

Of course, one should bear in mind that the framework informed by the results of behavioral genetic studies is probabilistic and predicated on a dimensional model of psychopathology. However, we believe this framework is useful for thinking about the way in which genes and the environment may contribute to childhood depression or anxiety. &

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